Title: Mitral Annular Plane Systolic Excursion: An Early Marker of Mortality in Severe COVID-19 Infection

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This is the author's manuscript of the work published in final edited form as:

Jarori, U., Maatman, T. K., Maatman, B., Mastouri, R., Sawada, S. G., & Khemka, A. (2020). Mitral Annular Plane Systolic Excursion: An Early Marker of Mortality in Severe COVID-19 Infection. Journal of the American Society of Echocardiography. https://doi.org/10.1016/j.echo.2020.08.012

Respiratory failure is a major cause of mortality among hospitalized patients with COVID-19 (1). Previous studies have shown that right ventricular (RV) dilation and reduced RV longitudinal strain are markers of poor outcome in this disease (2,3). COVID-19 can cause direct myocardial injury resulting in left ventricular (LV) systolic dysfunction and heart failure suggesting that assessment of LV function might also have prognostic value (4). Reduction of longitudinal systolic function assessed by mitral annular plane systolic excursion (MAPSE) is an early indicator of myocardial disease in various cardiac disorders (5). In this retrospective study, we investigated the prognostic value of MAPSE in patients admitted with respiratory failure related to COVID-19 infection.

One-hundred and nine patients were admitted to the ICU at IU Health hospitals with lab confirmed severe COVID-19 infections, defined as SpO2<94%, respiratory rate≥30 breaths per minute and P/F ratio ≤300 mmHg or need for mechanical ventilation. Of these, 68 patients that underwent transthoracic echocardiogram (TTE) based on clinical indication were included in the final analysis. Echocardiograms were performed using GE S70 and E95 (GE Healthcare, Milwaukee, Wisconsin, USA) and Phillips EPIQ (Philips Medical Systems, Andover, MA, USA) ultrasound systems. Images were acquired according to a limited COVID-19 protocol and measurements were performed as per American Society of Echocardiography guidelines. LV ejection fraction (EF) was measured by biplane Simpson's method. MAPSE was calculated as the average of septal and lateral mitral annular excursion measured in the apical 4-chamber view. Thirty-five of the 68 studies (52%) had sub-optimal image quality.

TTE was performed a median of 1 day (Inter-quartile range, 0-3 days) after hospital admission. Sixty-six patients (97%) required mechanical ventilation during hospitalization. Of these, 52 (79%) were on a ventilator at the time of echocardiography**.** Twenty-two patients (32%) died during hospitalization. Chi-square and Mann-Whitney U tests were used to compare clinical characteristics between survivors and those who died (Table 1). P-values <0.05 was considered significant. Increased age (p=0.018) and shock requiring vasopressors (p=0.033) were the only variables associated with mortality. The comparison of echocardiographic variables is shown in Table 2. Patients who died had significantly increased right atrial (RA) indexed volume (p=0.010) and lower MAPSE (p=0.006). There were trends towards lower LV EF and tricuspid annular excursion (TAPSE) in those who died. Among laboratory parameters, serum creatinine was significantly higher in those who died (p=0.032) [Supplementary Table 1]. Multivariable analysis was conducted using binary logistic regression incorporating variables significant on bivariate analysis. Shock requiring vasopressors (HR 9.2; 95% CI 1.4-59.3), MAPSE (HR 1.6; 95% CI 1.2-2.2), and RA indexed volume (HR 1.1; 95% CI 1.0-1.3) were found to be independently associated with mortality. MAPSE yielded an area under curve (AUC) of 0.72 with an optimal threshold of 1.0 cm by receiver operating characteristic curve analysis. The AUC for RA indexed volume was 0.61 with an optimal cutoff valve of 22.6 cm^3. When used in combination, RA

indexed volume and MAPSE enabled identification of high and lower risk groups. Mortality was 77% in the presence of either reduced MAPSE (<1.0 cm) or increased RA volume index (>22.6 cm^3). Survival was 84% in those who had both preserved MAPSE, and no significant RA enlargement.

MAPSE emerged as the only left heart parameter independently associated with increased mortality. Other parameters of left heart size and function were not significantly different between groups, although there was a trend towards lower EF in those who died. This suggests that MAPSE may enhance early assessment of LV myocardial injury in patients with severe COVID-19 infection. MAPSE is a validated measure of LV longitudinal function that likely correlates reasonably with longitudinal strain. Thus, in critically-ill patients where image quality is insufficient for accurate assessment of longitudinal strain, MAPSE may be a reasonable alternative. Additionally, RA enlargement was independently associated with mortality. In the setting of respiratory failure from COVID-19, RA enlargement may result from the combined effect of increasing pulmonary pressures, right ventricular systolic dysfunction, positive pressure ventilation, and fluid resuscitation. It is therefore not surprising that development of RA enlargement early in the hospital admission is a marker of later mortality. Although our study did not confirm the association between mortality and RV dilation or dysfunction, there was a trend towards lower TAPSE in patients that died.

There has been significant effort to identify early predictors of mortality including using modalities such as point of care ultrasound (6,7). In our study population of critically-ill patients with COVID-19, the presence of either reduced MAPSE or RA enlargement was associated with high risk of in-hospital mortality while those who had preserved MAPSE, and no RA enlargement had a high in-hospital survival rate. This suggests in combination, MAPSE and RA size can successfully risk stratify patients with severe COVID-19 infection early in their hospital course and may enable early institution of aggressive therapies for high risk patients.

The retrospective nature, small sample size and possible bias related to selective use of echocardiography are limitations of our investigation. Our findings suggest that assessment of longitudinal systolic function of the left heart using MAPSE in addition to evaluation of the right heart may yield accurate information for risk stratification of patients with severe COVID-19 infection early in their hospital course. Larger, prospective studies are needed to further define parameters that predict outcome in this disease.

REFERENCES:

[1] Churchill TW, Bertrand PB, Bernard S, Namasivayam M, Churchill J, Crousillat D, et al. Echocardiographic features of COVID-19 illness and association with cardiac biomarkers. J Am Soc Echocardiogr. 2020. [In Press]. https://doi.org/10.1016/j.echo.2020.05.028

[2] Argulian E, Sud K, Vogel B, Bohra C, Garg VP, Talebi S, et al. Right ventricular dilation in hospitalized patients with COVID-19 Infection. J Am Coll Cardiol Img 2020 May 15; [In Press]. doi.org/10.1016/j.jcmg.2020.05.010.

[3] Li Y, Li H, Zhu S, Xie Y, Wang B, He L, et al. Prognostic value of right ventricular longitudinal strain in patients with COVID-19. J Am Coll Cardiol Img 2020 Apr 28; [In Press]. doi.org/10.1016/j.jcmg.2020.04.014

[4] Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail 2020; 22:911-915. doi:10.1002/ejhf.1828.

[5] Hu K, Liu D, Herrmann S, Niemann M, Gaudron PD, Voelker W, et al. Clinical implication of mitral annular plane systolic excursion for patients with cardiovascular disease. Eur Heart J Cardiovasc Imaging 2013; 14:205-212. doi:10.1093/ehjci/jes240.

[6] Johri AM, Galen B, Kirkpatrick JN, Lanspa M, Mulvagh S, Thamman R. ASE Statement on Point-of-Care Ultrasound during the 2019 Novel Coronavirus Pandemic. J Am Soc Echocardiogr. 2020; 33:670-673. https://doi.org/10.1016/j.echo.2020.04.017

[7] Zhang L, Wang B, Zhou J, Kirkpatrick J, Xie M, Johri A. Bedside Focused Cardiac Ultrasound in COVID-19 from the Wuhan Epicenter: The Role of Cardiac Point-of-Care Ultrasound, Limited Transthoracic Echocardiography, and Critical Care Echocardiography. J Am Soc Echocardiogr. 2020; 33:676-682. https://doi.org/10.1016/j.echo.2020.04.004

Table 1. Baseline demographics, medical comorbidities, and clinical course of the overall cohort and each study group

Table 1.	**All Patients**	**Alive**	**Dead**	***P***
No. of Patients	**68**	**46 (68%)**	**22 (32%)**	
Demographic Information	**n (%)/mean ± SD**	**n (%)/mean ± SD**	**n (%)/mean ± SD**	
Age, years (range)	64±14 (31-87)	61±15 (31-86)	70±10 (47-87)	0.018*
Body Mass Index, kg/m^2	34.9±10.9	33.3±10.3	38.2±11.0	0.075
Sex				0.503
Male	41 (60)	29 (63)	12 (55)	
Female	27 (40)	17 (37)	10 (45)	
Race				0.944
Black	36 (53)	24 (52)	12 (55)	
White	28 (41)	19 (41)	9 (41)	
Other	4 (6)	3 (7)	1 (5)	
Hypertension	47 (69)	31 (67)	16 (73)	0.656
Dyslipidemia	41 (60)	26 (57)	15 (68)	0.358
Diabetes Mellitus	26 (38)	18 (39)	8 (36)	0.826
Tobacco Use	22 (32)	16 (35)	6 (27)	0.536
Coronary Artery Disease	18 (26)	12 (26)	6 (27)	0.917
Congestive Heart Failure	13 (19)	10 (22)	3 (14)	0.427
Chronic Kidney Disease	11 (16)	9 (20)	2 (9)	0.272
COPD	12 (18)	8 (17)	4 (18)	0.936
Asthma	10 (15)	5 (11)	5 (23)	0.196
Clinical Information				
Organ Failure				
Mechanical Ventilation	66 (97)	45 (98)	21 (95)	0.588
Shock Requiring Vasopressor	47 (69)	28 (61)	19 (86)	0.033*
Renal Replacement Therapy	15 (22)	8 (17)	7 (32)	0.180
ICU Days	13±8	14±8	10±6	------
Hospital Days	18±9	21±8	11±5	------

*Represents statistical significance with $P < 0.05$.

†SD, standard deviation; COPD, chronic obstructive pulmonary disease.

Table 2. Echocardiogram parameters of the entire cohort and a comparison between patients surviving and patients that died

Table 2.	**Cohort**	**Alive**	**Dead**	***P***
No. of Patients	**68**	**46 (68%)**	**22 (32%)**	
Echocardiogram Parameter	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	
LV Diastolic Volume (mL)	103±34	107±38	95±24	0.186
LV Systolic Volume (mL)	48±24	48±24	49±24	0.908
LV Ejection Fraction (%)	55±14	56±12	50±16	0.089
LVOT VTI (cm)	18±4	18±4	17±5	0.263
IVS thickness (cm)	1.1±0.2	1.1±0.2	1.1±0.2	0.886
LVPW thickness (cm)	1.0±0.2	1.0±0.2	1.1±0.2	0.719
LV Diastolic Diameter (cm)	4.6±0.8	4.7±0.8	4.6±0.8	0.699
LV Systolic Diameter (cm)	3.2±0.8	3.2±0.8	3.3±1.0	0.993
LV Basal Fractional Shortening	0.30±0.11	0.31±0.10	0.28±0.14	0.407
LA volume (indexed for BSA) (mL/m^2)	21.7±9.7	21.4±7.7	22.2±12.9	0.767
LA AP diameter (cm)	3.6±0.7	3.7±0.7	3.4±0.7	0.057
RV Basal Diameter (cm)	3.9±0.8	3.8±0.7	4.0±0.9	0.484
TAPSE (cm)	2.0±0.4	2.1±0.4	1.9±0.4	0.084
RV Diastolic Area (indexed for BSA) (cm^2/m^2)	10.2±3.1	10.1±2.8	10.6±3.6	0.566
RV Systolic Area (indexed for BSA) (cm^2/m^2)	6.4±2.5	6.2±1.9	7.0±3.2	0.260
RV FAC (%)	37.7±9.2	38.8±8.8	35.8±9.9	0.268
RA volume (indexed for BSA) (mL/m^2)	19.6±10.9	17.0±7.0	24.3±14.8	0.010*
RVOT VTI (cm)	14.3±4.1	14.4±3.9	14.0±4.8	0.778
E/e' lateral	8.9±5.0	9.3±5.5	8.1±3.5	0.395
E/e' septal	10.2±3.7	10.2±3.3	10.3±4.4	0.951
E/e' (Avg) (cm/s)	9.7±4.3	10.0±4.6	9.1±3.8	0.441
TR Jet Velocity (cm/s)	255±52	256±49	254±56	0.933
RAP (mmHg)	8.7±5.4	7.8±5.3	10.3±5.2	0.103
RVSP (mmHg)	34.0±12.0	31.3±13.2	37.1±9.9	0.213

PVR (WU)	2.2±0.9	2.1±0.9	2.5±0.8	0.274
MAPSE (cm)				
Lateral	1.3±0.3	1.3±0.3	1.1±0.3	0.004*
Septal	1.0±0.3	1.1±0.2	0.9±0.2	0.008*
Averaged	1.1±0.3	1.2±0.3	1.0±0.3	0.006*

*Represents statistical significance with $P < 0.05$.

†SD, standard deviation; LV, left ventricle; LVOT, left ventricular outflow tract; VTI, velocity time integral; IVS, interventricular septum; LVPW, left ventricular posterior wall; LA, left atrium; BSA, body surface area; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion; FAC, fractional area change; RA, right atrium; RVOT, right ventricular outflow tract; E, peak transmitral early diastolic inflow velocity; e', peak early diastolic longitudinal mitral annular velocity determined by color TDI; TR, tricuspid regurgitation; RAP, right atrial pressure; RVSP, right ventricular systolic pressure; PVR, pulmonary vascular resistance; MAPSE, mitral annular plane systolic excursion